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| APPLICATION NO. | FILING DATE | FIRST NAMED INVENTOR | ATTORNEY DOCKET NO. |
|---|---|---|---|
| 08/923,138 | 09/04/97 | KUCHERLAPATI R | CELL-4.8 |

HM12/0514

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| EXAMINER | |
|---|---|
| HAUDA,K | |
| **ART UNIT** | **PAPER NUMBER** |
| 1632 | 15 |

**DATE MAILED:** 05/14/99

**Please find below and/or attached an Office communication concerning this application or proceeding.**

**Commissioner of Patents and Trademarks**

| Office Action Summary | Application No. 08/923,138 | Applicant(s) Kucherlapati et al. |
|---|---|---|
| | Examiner Karen M. Hauda | Group Art Unit 1632 |

☒ Responsive to communication(s) filed on *Sep 4, 1997* .

☒ This action is **FINAL.**

☐ Since this application is in condition for allowance except for formal matters, **prosecution as to the merits is closed** in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

A shortened statutory period for response to this action is set to expire *3* month(s), or thirty days, whichever is longer, from the mailing date of this communication. Failure to respond within the period for response will cause the application to become abandoned. (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

**Disposition of Claims**

☒ Claim(s) *1-45* is/are pending in the application.

Of the above, claim(s) *4-45* is/are withdrawn from consideration.

☐ Claim(s) _____ is/are allowed.

☒ Claim(s) *1-3* is/are rejected.

☐ Claim(s) _____ is/are objected to.

☐ Claims _____ are subject to restriction or election requirement.

**Application Papers**

☐ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.

☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

☐ The proposed drawing correction, filed on _____ is ☐approved ☐disapproved.

☐ The specification is objected to by the Examiner.

☐ The oath or declaration is objected to by the Examiner.

**Priority under 35 U.S.C. § 119**

☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

☐ All ☐ Some* ☐ None of the CERTIFIED copies of the priority documents have been

☐ received.

☐ received in Application No. (Series Code/Serial Number) _____ .

☐ received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

*Certified copies not received: _____ .

☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

**Attachment(s)**

☐ Notice of References Cited, PTO-892

☐ Information Disclosure Statement(s), PTO-1449, Paper No(s). _____

☐ Interview Summary, PTO-413

☐ Notice of Draftsperson's Patent Drawing Review, PTO-948

☐ Notice of Informal Patent Application, PTO-152

*--- SEE OFFICE ACTION ON THE FOLLOWING PAGES ---*

## DETAILED ACTION

The request filed on September 4, 1997, paper # 14 for a Rule 62 continuation based on parent Application No. 08/430,938 is acceptable and a File Wrapper Continuation has been established.

Applicant's response fails to address the rejections of record contained in the office action mailed March 4, 1997, paper # 11. Therefore, for the reasons of record all rejections are maintained as set out in the office action mailed March 4, 1997, paper # 11 and re-iterated below for the convenience of applicants.

This application should be reviewed for errors. An example of such an error occurs on page 9, line 2 wherein the citation is absent.

Applicant's election with traverse of Group I, in Paper No. 9 is acknowledged. The traversal is on the ground(s) that, with respect to I and II, because the immunization steps of Group I are used to make B cells that have the polynucleotides used in the method of Group II and that therefore these methods should not be restricted into separate groups. This is not found persuasive because the polynucleotides used in the method of group II may be made by other and materially different processes, such as chemical synthesis, for example.

Applicants have traversed the restriction of Groups I, II and IV but have not presented arguments.

Applicants have traversed the restriction of Groups III and IV but have not presented arguments.

Applicants have traversed the restriction of Groups I, II and III for essentially the same reasons as that presented for I and II, above. This argument is not found persuasive for reasons set forth, above.

The requirement is still deemed proper and is therefore made FINAL.

Claims 1-3 are active and examined in this Office action, claims 4-45 being withdrawn from examination as being directed to a non-elected invention.

The incorporation of essential material by reference to a foreign application or foreign patent or to a publication inserted in the specification is improper. Applicant is required to amend the disclosure to include the material incorporated by reference. The amendment must be accompanied by an affidavit or declaration executed by the applicant, or a practitioner representing the applicant, stating that the amendatory material consists of the same material incorporated by reference in the referencing application. *In re Hawkins*, 486 F.2d 569, 179 USPQ 157 (CCPA 1973); *In re Hawkins*, 486 F.2d 579, 179 USPQ 163 (CCPA 1973); *In re Hawkins*, 486 F.2d 577, 179 USPQ 167 (CCPA 1973).

The attempt to incorporate subject matter into this application by reference to PCT application WO 94/02602 is improper because the claimed mice are only described in the PCT

application but are essential to practicing the invention as claimed. Incorporation by reference may only occur on application on which the issue fee has been paid or on issued US patents.

The following is a quotation of the first paragraph of 35 U.S.C. § 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-3 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. The specification teaches the production of IgM immunoglobulins wherein the human heavy chain constant region is mu and further teaches the production of murine gamma, not human gamma, presumably by trans-switching. The specification does not enable one of skill to make human IgG in the transgenic mouse system. The specification fails to disclose, or enable one of skill to make, the transgene containing the essential nucleotide sequences necessary in the transgene in order for class switching to occur. Therefore, the claims must be limited to IgM having a human variable region, human mu constant region, human kappa chains and, if IgG, murine gamma constant regions. At the time the claimed invention was made, 4/27/95, applicants did not have in their possession the transgene capable of undergoing class switching from IgM to IgG. Trans-switching, the switching of the variable region from one constant region to another constant region, was known to occur in the art. For example, a human variable region could switch from the human mu chain constant region to the murine mu constant region. Isotype switching involves the switching of the human variable region to a constant region of any one of several other isotype classes, contained on the same gene or nucleotide sequence, the first constant region being the gamma constant region. The declaration by Dr. Cox, of record in US patent 5,545,806 (application serial no. 07/990,860; Lonberg et al.) and now publicly available, discloses "I am

unaware of any reports of successfully cloning intact a Not I fragment containing the region between the human delta and gamma-3 genes or any other restriction fragment containing this region in a YAC vector". Dr. Cox specifically points to applicants' own work (Nature Genetics 3: 88, 1994; Nature Genetics 7: 13, 1994; and Nature Genetics 7:162, 1994) and declares that cloning of the regions necessary for class switching was not accomplished by applicants. In view of the foregoing, the specification is not enabling for any constant region other than human mu and the claims must be so limited.

In addition, the claims claim "analogs thereof" and the specification fails to disclose the transgenic mice producing only immunoglobulin fragments, presumably the "analogs thereof". The specification discloses mice producing entire immunoglobulin molecules produced from xenomice, the genomes of which are not disclosed herein. The specification does not enable one of skill to produce immunoglobulin fragments in mice containing only intact immunoglobulin genes. The specification fails to disclose how the intact immunoglobulin molecules, once produced in vivo, are manipulated in vivo to produce immunoglobulin fragments. Although the claims claim a method to produce an immunoglobulin analog, the xenomice, which are not enabled by the specification for reasons disclosed above, apparently do not contain the genes encoding only the immunoglobulin analog. Further, the specification fails to enable knockout of the variable region genes per se. Claim 1 specifically claims that the nonhuman animal is incapable of producing endogenous heavy or light chain variable regions. Lacking details of the xenomouse construction, the specification is not enabling for the invention as claimed. Applicants presumably intend that the variable region expression is prevented by knockout of the J region segments, which inhibits expression of the entire chain, not just the variable region.

Claims 1-32 are rejected under 35 U.S.C. 112, second paragraph, as failing to set forth the subject matter which applicant(s) regard as their invention. The phrase "analog thereof" is vague and unclear since the modification intended is not apparent. While the claims may be interpreted in light of the specification, they are not so limited and the intended metes and bounds of "analog

thereof" are indeterminate. Analogs may be nucleotide variants, for example, of the Fab portions or single chain Fvs. Although all are known in the art, which one or ones applicants are intending to claim is not apparent. Further, the claim appears to be incomplete since the preamble produces an immunglobulin while the indented paragraph produces only human immunoglobulin variable regions while the immunoglobulin or analog is recovered in the final step.

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1-3 are rejected under 35 U.S.C. 103 as being unpatentable over Surani (USPN 5,545,807) taken with Bruggemann et al. and Krimpenfort (USPN 5,591,669). Surani discloses trangenic mice having inserted into their genomes DNA comprising human Vh, human Dh, human Jh segments and human mu segments in unrearranged germline configuration such that upon rearrangement of the germline segments, heavy chains containing totally human V regions may be one of the heavy chains produced, the other heavy possibility being a chimeric heavy chain containing a murine variable region. Surani further discloses a method of producing immunoglobulins to a particular antigen comprising administering the antigen to the transgenic mouse and obtaining the immunoglobulins from the cells or body fluids of the mouse. Surani

further discloses obtaining immunoglobulins from the B cells of the mouse in addition to producing monoclonal antibodies comprising fusing the B cells with a suitable myeloma fusion partner to produce hybridomas, culturing the hybridomas under suitable conditions for production of monoclonal antibodies and recovering the produced chimeric mouse-human monoclonal antibodies. Surani discloses producing and recovering polyclonal antibodies from the mouse. Surani additionally discloses insertion of a human antibody gene construct containing a rearranged variable region and a human constant region. Surani differs from the claims in that the reference fails to disclose a mouse having inactivated endogenous immunoglobulin variable region genes. However, the secondary references, Bruggemann and Krimpenfort, cure the deficiency. Bruggemann discloses the desirability of producing human immunoglobulins in a mouse incapable of expressing endogenous mouse immunoglobulins. Krimpenfort discloses inactivation of endogenous mouse immunoglobulin gene expression by "knocking out" the endogenous genes via homologous recombination. Krimpenfort further discloses that in order to inactivate endogenous immunoglobulin gene expression, the variable region of immunoglobulin genes may be targeted as well as the constant region or the J region (column 8, lines 10-16).

It would have been obvious to one of ordinary skill to modify the mouse the mouse of Surani by knocking out expression of the variable region as suggested by Krimpenfort in view of the suggestions by Bruggemann of the desirability of producing human immunoglobulins or chimeric immunoglobulins in mice incapable of expressing endogenous immunoglobulin genes. Bruggemann provides the motivation to abolish expression of endogenous immunoglobulin genes while Krimpenfort provides the reasonable expectation of success in being able to abolish of expression of endogenous immunoglobulin genes.

Accordingly, the modification of the method of Surani, teaching expresion of human immunoglobulin mu chains in transgenic mice, by inactivating endogenous immunoglobulin gene expression as taught by Krimpenfort in order to produce transgenic mice expressing human immunoglobulins and incapable of expressing endogenous murine immunoglobulins was within the ordinary skill in the art at the time the claimed invention was made. From the teachings of the

references, it is apparent that one of ordinary skill would have had a reasonable expectation of success in producing the claimed invention, and therefore, the invention as a whole is prima facie obvious.

Claims 1-3 are rejected under 35 U.S.C. 103(a) as being unpatentable over Krimpenfort (USPN 5,591,669)taken with Lonberg(USPN 5,545,608). Krimpenfort discloses making transgenic mice having the endogenous immunoglobulin genes inactivated by targeting constructs and therefore incapable of expressing endogenous immunoglobulins. Krimpenfort differs from the claims in that the reference fails to disclose further addition of a transgene encoding human immunoglobulin genes. However, the secondary reference, Lonberg, cures the deficiency. Lonberg discloses a method for producing human immunoglobulins to a specific antigen from a transgenic mouse comprising administering the antigen and collecting the produced immunoglobulins. Both Krimpenfort and Lonberg disclose transgenic mice having the endogenous immunoglobulin heavy chain and light chain gene loci inactivated and therefore mice incapable of producing endogenous immunoglobulins (column 28, lines 34-end and continued in column 29). Lonberg discloses that rearranged or unrearranged V segments may be isolated with or without flanking sequences (column 25, lines 60-64) and further discloses production of polyclonal antibodies. Lonberg discloses the motivation for making transgenic mice expressing human immunoglobulin genes and having the murine endogenous immunoglobulin loci inactivated and further discloses mice making human heavy chains in a endogenous immunoglobulin gene knock-out background. See table 9, column 80. Krimpenfort is cited to disclose the knockout technique and that such was old and well known in the art at the time the claimed invention was made. Both Krimpenfort and Lonberg provide the reasonable expectation of success in obtaining inactivation of endogenous immunoglobulin gene expression in transgenic mice, while Lonberg discloses both the knockout condition and the insertion of human immunoglobulin genes into the murine genome for purposes of making human antibodies to human antigens.

Accordingly, the modification of the method of Krimpenfort by adding a transgene encoding human immunoglobulins as taught by Lonberg was within the ordinary skill in the art at

the time the claimed invention was made. From the teachings of the references, it is apparent that one of ordinary skill would have had a reasonable expectation of success in producing the claimed invention, and therefore, the invention as a whole is prima facie obvious.

No claim is allowed.

This is a continuation of applicant's earlier Application No. 08/430,938. All claims are drawn to the same invention claimed in the earlier application and could have been finally rejected on the grounds and art of record in the next Office action if they had been entered in the earlier application. Accordingly, **THIS ACTION IS MADE FINAL** even though it is a first action in this case. See MPEP § 706.07(b). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no, however, event will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

This application contains claims 4-45 drawn to an invention nonelected with traverse in Paper No. 9. A complete reply to the final rejection must include cancelation of nonelected claims or other appropriate action (37 CFR 1.144) See MPEP § 821.01.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Karen M. Hauda whose telephone number is (703) 305-6608.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Brian R. Stanton, may be reached at (703) 308-2035.

Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist whose telephone number is (703) 308-2801.

**The Group and/or Art Unit location of your application in the PTO has changed. To aid in correlating any papers for this application, all further correspondence regarding this application should be directed to Group Art Unit 1632.**

Papers related to this application may be submitted to Group 160 by facsimile transmission. Papers should be faxed to Group 160 via the PTO Fax Center located in Crystal Mall 1. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The CM1 Fax Center number is or (703) 305-3014 or (703) 308-4242.

Karen M. Hauda
Patent Examiner
May 11, 1999

BRIAN R. STANTON, PH.D
PRIMARY EXAMINER